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WEEKLY REPORT

For Week Ending October 25, 1969

ACIP RECOMMENDATIONS 1969

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SUPPLEMENT

Collected Recommendations of the Public Health Service Advisory Committee on Immunization Practices

The Public Health Service Advisory Committee on Immunization Practices has in the last 5 years made recommendations concerning the use of vaccines and other biologics in the prevention of 16 diseases. Each statement by the ACIP is regularly published in the *Morbidity and Mortality Weekly Report* upon completion or revision.

The full series of recommendations has never been printed as a single document. However, it was felt that a supplement to the *MMWR* incorporating all of the existing ACIP recommendations would be a useful reference.

The Committee has reviewed all of its statements within the past several months. Only minor revisions and editorial changes were made. No substantive modifications resulted from this annual review. Each of the statements carries the dates of original publication and past revisions.

For the first time, a brief list of selected references is appended to each statement. These bibliographies are not meant to be definitive, but are a starting point for more extensive review of the pertinent literature on the disease, the vaccine, and its appropriate uses.

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PUBLIC HEALTH SERVICE
ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

Since its establishment in 1964, the Public Health Service Advisory Committee on Immunization Practices has prepared recommendations on the principal biologics used in the United States. Some of its earlier statements have been modified as the incidence of disease has changed and as additional information about the biologics has been accumulated. The ACIP reviews all statements annually and revises or confirms the recommendations according to current findings.

As statements are developed or revised, they appear first in the *Morbidity and Mortality Weekly Report* and are often reprinted elsewhere. Although intended primarily for use in public health, their broader applicability is acknowledged. Therefore, special attention is paid to the established practices in medical specialties where immunizing agents are commonly used. Minor differences in emphasis have not been felt to compromise the goal of achieving immunity in vaccinees.

The Advisory Committee on Immunization Practices was established by the Surgeon General of the Public Health Service to advise him on the status of immunizing agents and their use for optimal benefit. The Committee is sponsored by the National Communicable Disease Center, and its membership is drawn from the fields of public health, medicine, and research. *Ex officio* membership is from government agencies with particular responsibility and involvement in licensing biologics and in civilian immunization programs. Special consultants regularly join the ACIP in its deliberations. Surveillance reviews, laboratory and field investigations, and other support are provided by NCDC.

Members of the ACIP at the time of the 1969 review were:

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CHOLERA VACCINE

INTRODUCTION

Cholera generally occurs in endemic and epidemic form only in South and Southeast Asia. In recent years, however, it has also been epidemic in certain areas of the Middle East.

Infection is acquired from contaminated water or food. It is believed to result from personal contact only in rare instances.

CHOLERA VACCINE

Various cholera vaccines have been widely used, but until recently their efficacy was unproved. Carefully controlled field studies have now clearly demonstrated the effectiveness of current vaccines against both the classical and El Tor strains of cholera vibrios. However, severe cases of cholera have occurred in vaccinated persons.

The duration of immunity induced by vaccine is relatively brief. Antibody titers reach a peak within 4 weeks of vaccination and are maintained for about 3 months. Protection against disease seems to last no more than 6 months after the primary series or a booster dose.

Vaccine available in the United States is prepared from a combination of inactivated suspensions of classical Inaba and Ogawa strains of cholera vibrios grown on agar or in broth and preserved with phenol.

VACCINE USAGE

Vaccination for International Travel

A primary vaccination or a booster dose within the previous 6 months is generally required for persons traveling to or from countries with cholera.* Vaccination requirements are published annually by the World Health Organization and summarized by the Public Health Service in its booklet *Immunization Information for International Travel* (PHS Publication No. 384). Because cholera sometimes reappears in countries free of the disease for several years, travelers should seek up-to-date information to determine the need for a valid International Certificate of Vaccination.

Physicians administering vaccine to travelers should emphasize that an International Certificate of Vaccination must be validated for it to be acceptable to quarantine authorities. Validation can be obtained at most city, county, and State health departments. Failure to secure validation can cause travelers to be revaccinated or quarantined during the course of travel. The Certificate remains valid for 6 months.

The traveler's best protection against cholera, as well as against many other enteric diseases, is to avoid potentially contaminated food and water. Persons following the usual tourist itinerary through countries reporting cholera and using standard accommodations run virtually no risk of acquiring cholera.

Primary Immunization

Injections may be given subcutaneously or intramuscularly.

For travelers vaccinated in the United States, a single 0.5 ml dose of cholera vaccine is considered adequate to satisfy the International Sanitary Regulations. The single dose for children is proportionately smaller (see table below).

Two doses of cholera vaccine, 0.5 ml and 1.0 ml, preferably given a month or more apart, are recommended for adults traveling or working in areas where cholera is epidemic or known to be endemic and living under conditions in which sanitation is less than adequate. The doses for children are suggested in the summary table. A two-dose schedule of vaccination is also advisable for persons working with cholera vibrios in the laboratory.

Booster Doses

Booster injections should be given every 6 months as long as the likelihood of exposure exists. In areas where cholera only occurs in a 2 to 3 month "season," protection is optimal when the booster dose is given at the beginning of the season. The primary series need never be repeated for booster doses to be effective.

Summary

The following table summarizes the recommended doses for primary and booster vaccination:

Dose Number	Age (Years) Under 5	5 10	Over 10
1	0.1 ml	0.3 ml	0.5 ml
2 & Boosters	0.3 ml	0.5 ml	1.0 ml

Reactions

Vaccination often results in discomfort at the site of injection for one or more days. The local reaction may be accompanied by fever, malaise, and headache.

Contraindication

Rarely, severe reactions of various kinds follow administration of cholera vaccine. If one experiences such a reaction, revaccination is not advisable. Most governments will permit such an individual to proceed provided he carries a physician's statement of the medical contraindication. However, any inadequately vaccinated traveler coming from an infected area may be quarantined or placed under surveillance for 5 days.

*For a current listing, consult the most recent issue of the World Health Organization's Weekly Epidemiological Record.

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DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE

INTRODUCTION

Routine immunization against diphtheria, tetanus, and pertussis during infancy and childhood has been widely advocated and generally practiced in the United States in the past 25 years. Its effectiveness is reflected in decreasing incidence of and mortality from these three diseases.

Diphtheria

There has been continuing decline in the annual incidence of diphtheria since World War II, and diphtheria is now a rare disease in many parts of the United States. However, localized outbreaks continue to appear with some severe cases and a case-fatality ratio often greater than 10 percent. In 1968, 260 cases were reported.

Although most diphtheria cases occur in children, cases and deaths are reported in all age groups. Nearly all cases occur in inadequately immunized individuals. Diphtheria toxoid, when administered according to recommended schedules, prevents diphtheria mortality and greatly reduces clinical illness and complications. Following adequate immunization, protective levels of antitoxin appear to persist for 10 years or more.

Tetanus

Although its incidence in the United States has declined in recent years, tetanus remains a public health problem which can only be prevented by universal active immunization. In 1968, 163 cases of tetanus were reported, the majority in unimmunized adults; the median age was 48, excluding neonates. The national death-to-case ratio was more than 65 percent. Thus, primary immunization and periodic boosters must be emphasized not only for children but also for all adults. Adequate immunization with tetanus toxoid provides effective and durable protection against disease and eliminates the need for passive immunization at the time of injury. Universal active immunization will ensure protection against the significant proportion of tetanus infections which follow trivial injury or through unrecognized portals of entry.

Tetanus toxoid is an almost ideal immunizing agent. It is highly effective, has almost no side effects, and provides long-lasting protection. Because there is no natural immunity to the ubiquitous tetanus organism and no general contraindications to tetanus toxoid, the importance of immunization is universal.

Pertussis

The high mortality from pertussis in infancy is the major rationale for immunization early in life. The disease is highly communicable, and attack rates up to 90 percent are reported among unimmunized household contacts. Most cases occur in infants and young children. In 1967, nearly three-fourths of pertussis deaths occurred in infants less than a year old – some 40 percent of the total occurred in infants 3 months of age or less.

Pertussis immunization is effective in reducing both cases and deaths. Mortality from pertussis has declined dramatically with increasingly widespread use of standardized pertussis vaccines beginning in the mid 1940's. Because the incidence of and mortality from pertussis decrease with age, pertussis immunization is not generally required past age 6 years or after entry to elementary school.

Severe central nervous system reactions, occasionally with permanent sequelae or death, occur very rarely after administration of pertussis vaccine. Their incidence, however, is much lower than the incidence of similar serious reactions following the disease itself.

PREPARATIONS USED FOR IMMUNIZATION

Diphtheria and tetanus toxoids are prepared by formaldehyde treatment of the respective toxins. Pertussis vaccine is made from a killed suspension of bacteria or a bacterial fraction.

The toxoids and pertussis vaccine are available in both fluid and adsorbed forms. Comparative tests have shown that the adsorbed toxoids are clearly superior in stimulating high antibody titers and achieving durable protection. The promptness of antibody responses to booster doses of either fluid or adsorbed toxoids is not sufficiently different to be of clinical importance. Therefore, adsorbed toxoids are the agents of choice for both primary and booster immunization.

These three antigens are available in various combinations and concentrations for specific purposes. Three preparations are important for public health use.

1. Diphtheria and Tetanus Toxoids and Pertussis Vaccine (DTP)
2. Tetanus and Diphtheria Toxoids, Adult Type (Td)
3. Tetanus Toxoid (T)

All preparations contain comparable amounts of tetanus toxoid, but the diphtheria component in the adult type of tetanus and diphtheria toxoids (Td) is only about 15 to 20 percent of that contained in the standard DTP preparation used in infants and young children.

VACCINE USAGE

Schedule and Dose

Recommendations are based upon immunologic and epidemiologic considerations, taking into account the possibly increased risks of exposure at school entrance. Since the concentration of antigens varies in different manufacturers' products, the labeling provides specific information on the proper volume of a single dose.

Primary Immunization

Children 2 months through 6 years: The recommended dose of **DTP** given intramuscularly on **three** occasions at 4 to 6 week intervals with a reinforcing dose approximately 1 year after the third injection. Ideally, immunization is begun at age 2 to 3 months or at the time of a 6-week "check-up" if such timing is an established routine.

Schoolchildren and adults: The recommended dose of **Td*** given intramuscularly or subcutaneously on **two** occasions at 4 to 6 week intervals with a reinforcing dose approximately 1 year after the second.

Booster Doses

Children 3 through 6 years (Preferably at time of school entrance – kindergarten or elementary school): The recommended dose of **DTP** intramuscularly.

Thereafter and for all other persons: The recommended dose of **Td** intramuscularly or subcutaneously every 10 years. (If a dose is administered sooner as part of wound management – see specific recommendations – the next booster is not needed for another 10 years.) More frequent booster doses are not indicated and may be associated with increased frequency and severity of reactions.

TETANUS PROPHYLAXIS IN WOUND MANAGEMENT

An important part of the management of wounds is prevention of tetanus. The physician is then often faced with questions of using tetanus toxoid for active protection and Tetanus Immune Globulin (Human) (TIG) or tetanus antitoxin of animal origin for passive protection. Available evidence demonstrates that complete primary immunization with tetanus toxoid (initial doses plus reinforcing dose) provides a very long-lasting basis for active protection against tetanus. Therefore, passive protection need be considered only when the patient has no valid history of any previous tetanus toxoid. This liberal interpretation is justifiable in view of evidence that persons who have previously received even one dose of tetanus toxoid will respond adequately to a single booster, even after an interval of many years.

The following outline is a conservative guide to active and passive tetanus immunization in wound management. It presumes a **reliable** knowledge of the patient's immunization history. (Considerable evidence indicates that immunity often persists very much longer than the specified 1 year interval; but until this observation is established conclusively, the 1 year interval is reasonable for general purposes.)

1. Primary immunization or last booster dose less than 1 year before injury: No tetanus prophylaxis required.

2. Primary immunization or last booster dose more than 1 year before injury: The recommended single dose of **Td**† intramuscularly or subcutaneously.

3. Incompletely immunized: Complete primary immunization.

4. Unimmunized or immunization history uncertain: Initiate primary immunization.

The decision to administer concomitant passive prophylaxis in this case will depend upon medical judgment after evaluating such factors as location of wound, its type and severity, the degree and kind of contamination, and the time elapsed since injury. If passive therapy is to be used, TIG is preferable. It offers the advantages of a longer period of protection and freedom from undesirable reactions. The currently recommended prophylactic dose of TIG is 250 units for wounds of average severity. When used concurrently, tetanus toxoid and globulin should be given in separate syringes at separate sites.

Should TIG be unavailable, equine or bovine antitoxin may be used, bearing in mind the risk that serious reactions may follow injections of animal serum. The usual dose is 3,000 to 5,000 units. Its administration should always be preceded by careful screening for sensitivity in accordance with instructions furnished with the antitoxin by the manufacturer.

*Td is considered the agent of choice for immunization of school-age children on the basis of data regarding its adequacy in primary immunization of older children and adults and because of increasing reactions to full doses of diphtheria toxoid with age. Such reactions are not uncommon from about age 6 in the southern United States, to 10 or 12 in the northern portions of the country. The use of Td obviates the need for Schick or Moloney testing prior to immunization.

† If there is any reason to suspect hypersensitivity to the diphtheria component, tetanus toxoid (T) should be substituted for Td (adult type).

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IMMUNE SERUM GLOBULIN FOR PREVENTION OF VIRAL HEPATITIS

(Infectious Hepatitis and Transfusion-Associated Hepatitis)

INFECTIOUS HEPATITIS

The agent that causes human infectious hepatitis has not yet been identified but is presumed to be a virus. No vaccine is available. Administration of Immune Serum Globulin (ISG)* to exposed persons can, however, afford a high degree of protection against infectious hepatitis. ISG substantially reduces the frequency of overt clinical disease, although inapparent infection may occur. Following such infection, lifelong active immunity is thought to develop.

Patients with infectious hepatitis have been shown to excrete virus in stool as much as 2 to 3 weeks before and 2 weeks after onset of jaundice. Viremia has been demonstrated approximately 2 weeks before and less than 1 week after onset of jaundice.

Transmission of the disease is principally by the fecal-oral route and is most likely to occur under conditions of inadequate sanitation or close contact with infected individuals. Direct person-to-person spread of infection otherwise is unusual. Transmission is also possible by the parenteral route. The incubation period of infectious hepatitis is relatively long, in most cases between 15 and 50 days (average 25 to 30 days).

IMMUNE SERUM GLOBULIN

ISG is prepared for intramuscular injection from large pools of plasma (1,000 or more donors) obtained from venous and/or placental blood. The product is a 16.5 percent solution of globulin prepared by cold alcohol fractionation. Serum hepatitis has not been transmitted by ISG of this type.

ISG FOR PREVENTING INFECTIOUS HEPATITIS

The decision to administer ISG should be based on assessment of the epidemiologic circumstances – specifically, whether the exposure could result in infection. The administration of ISG is relevant when there is: 1) definite exposure to a known case or source of infection, or 2) anticipated continuous or intermittent exposure.

ISG given after known exposure should be given as soon as possible. Its prophylactic value decreases as time

*Official name: Immune Serum Globulin (Human). Poliomyelitis Immune Globulin (Human) is an equivalent product and may also be used; other immune globulin products are not suitable.

increases after exposure. The use of ISG more than 5 to 6 weeks after exposure is not indicated.

Dosage

The dosage patterns of ISG in common use have been derived primarily from field and clinical observations. Data from these observations provide operational guidelines on which to base recommendations.

Under most conditions of exposure, protection has been afforded by giving 0.01 ml of ISG per pound of body weight (0.01 ml/lb or approximately 0.02 ml/kg). This dosage may be conveniently simplified (Table 1):

Table 1
Guidelines for ISG Prophylaxis of Infectious Hepatitis for General Use

Person's Weight (lb)	ISG Dose (ml)*
up to 50	0.5
50-100	1.0
over 100	2.0

*Within limits, larger doses of ISG provide longer-lasting but not necessarily more protection. Higher doses are, therefore, used under certain circumstances (See Institutional Contacts and Travelers to Foreign Countries).

Individual Recommendations

Household contacts: There is good evidence that close personal contact, such as occurs among permanent or even temporary household residents, is important in spreading infectious hepatitis. Secondary attack rates are high for household contacts, particularly children and teenagers. Although secondary attack rates are somewhat lower for adults, their illnesses tend to be more severe. For these reasons, ISG is recommended for all household contacts who have not already had infectious hepatitis.

School contacts: Although the highest incidence of hepatitis is among school-age children, contact at school is usually not an important means of transmitting this disease. Therefore, routine administration of ISG is not indicated for pupil or teacher contacts of a case. However, when epidemiologic study has clearly shown that school or classroom contact is responsible for continued transmission of disease, it is reasonable to administer ISG to individuals at risk.

Institutional contacts: In contrast to schools, conditions favoring transmission of infectious hepatitis exist in institutions such as prisons and facilities for the mentally retarded. Sporadic cases as well as epidemics have frequently been reported in such institutions. ISG administered to patient and staff contacts of cases in the doses shown in Table 1 effectively limited the spread of disease in these circumstances.

Where infectious hepatitis exists endemically, particularly in very large institutions with high rates of admission and discharge, residents and staff personnel may be subject to frequent and continuing exposure. Under these conditions, use of ISG has not resulted in eradication of hepatitis. However, it has been shown to provide temporary protection when administered in doses of 0.02 to 0.05 ml/lb at the time of admission or employment. It may be necessary to readminister ISG in the same dose after 6 months if the risk is felt to persist.

Hospital contacts: Routine prophylactic administration of ISG to hospital personnel is not indicated. Emphasis should be placed on sound hygienic practices. Intensive, continued education programs pointing out the risks of exposure to infectious hepatitis and the recommended precautions should be directed toward hospital personnel who have close contact with patients or infectious materials.

For those accidentally inoculated with blood or serum of patients with hepatitis, the appropriate prophylactic dose of ISG is that recommended in Table 1. There is no reason to give a larger dose because ISG appears to be effective in preventing only infectious hepatitis, not transfusion-associated (serum) hepatitis (See Transfusion-Associated Hepatitis).

Office and factory contacts: Routine administration of ISG is not indicated for persons in the usual office or factory situation exposed to a fellow worker with hepatitis.

Common source exposures: When a vehicle, such as food or water, is identified as a common source of infection of multiple hepatitis cases, administration of ISG should be considered for all those exposed to the source.

Pregnancy: Current information does not indicate that pregnancy in itself should alter the recommendations for ISG prophylaxis.

Travelers to foreign countries: The risk of infectious hepatitis for U.S. residents traveling abroad varies with living conditions and the prevalence of hepatitis in the areas to be visited. Travelers may be at no greater risk than in the United States when their travel involves ordinary tourist activities and little exposure to uncooked foods or water of uncertain quality. For these travelers, ISG is not recommended.

For travelers visiting areas where hepatitis is a major health problem who may be exposed to infected persons and to contaminated food and water, there is increased risk of acquiring hepatitis. A single dose of ISG is recommended for them as shown in Table 2, which gives guidelines for U.S. residents traveling in foreign countries. (Large geographic areas have been defined for ease of interpretation and because information is inadequate to permit developing more precise boundaries.)

For individuals who reside abroad in areas where hepatitis is common, the risk of hepatitis is greatly increased and appears to continue so for years. Experience has shown that regular administration of ISG offers at

least partial protection against hepatitis. It is recommended that prophylactic ISG be repeated every 6 months at doses indicated in Table 2.*

Table 2
Guidelines for ISG Prophylaxis of Infectious Hepatitis for U.S. Residents Traveling or Living in Foreign Countries*
(See text for additional details)

Area	Person's Weight (lb)	Short-Term Travel (1-2 months) ISG Dose (ml)	Extended Travel or Residence (3-6 months)** ISG Dose (ml)
Africa			
Asia			
North America			
Central America	up to 50	0.5	1.0
Mexico (Rural)	50-100	1.0	2.5
Pacific Region			
Philippine Islands	over 100	2.0	5.0
South Pacific Islands			
South America			
Europe			
North America			
Canada			
Caribbean Islands			
Mexico (Urban)	Routine ISG prophylaxis is not indicated		
Pacific Region			
Australia			
Japan			
New Zealand			

*In all travel, care should be exercised in consuming uncooked foods and water of uncertain quality.
**Repeat every 6 months of travel or residence.

Reactions

Intramuscular administration of ISG rarely is followed by adverse reactions. Discomfort may occur at the site of injection, especially when larger volumes are used. A few instances of hypersensitivity have been reported, but in view of the very large number of persons who have received ISG, the risk is exceedingly small.

ISG should not be administered intravenously because of the danger of severe reactions.

Antibody against gamma globulin may appear following administration of ISG although its clinical significance is unknown. When ISG is indicated for prophylaxis of infectious hepatitis, this theoretical consideration should not preclude its administration.

*Some agencies have used up to 0.05 ml/lb each 5 to 6 months rather than the 5 ml for adults recommended here.

TRANSFUSION-ASSOCIATED HEPATITIS

The risk of transmitting viral hepatitis by blood transfusion is a serious and continuing problem. Several reports indicate that the incidence of clinical hepatitis is greater among recipients of blood obtained from certain categories of donors. The risk also becomes greater as the number of transfusions increases. Furthermore, the case-fatality rate of transfusion-associated hepatitis increases with advancing age.

Evidence has been advanced both for and against the effectiveness of ISG as prophylaxis of transfusion-associated hepatitis. Although some investigators have reported that 10 ml of ISG at the time of transfusion and again 1 month later reduced the number of cases, other equally careful studies have not substantiated this claim. Existing evidence provides no adequate basis for recommending that ISG be given routinely to recipients of blood transfusions.

Among the means of effectively lowering the incidence of transfusion-associated hepatitis are: careful selection of donors, development of central registries of known or suspect carriers, and use of blood and potentially icterogenic blood products only when necessary.

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INFLUENZA VACCINE—1969-70

INTRODUCTION

The nationwide epidemic of A2 influenza in the United States in the fall and winter of 1968-69 showed the impact of a major antigenic change in the prevalent influenza viruses. The Hong Kong strain responsible for the epidemic was the most distinctive variant among A2 influenza viruses identified since initial appearance of the A2 sub-type in 1957. The 1968-69 epidemic highlighted again the problems that are encountered in rapidly developing and producing sufficient quantities of vaccine incorporating a new antigen.

Forty-four States reported widespread outbreaks of Hong Kong strain influenza; in six, involvement was less extensive. In all nine geographic divisions of the country, excess pneumonia and influenza mortality peaked sharply in early January 1969.

In December 1968, Washington State reported an outbreak of type B influenza concurrent with Hong Kong strain A2. In January and February 1969, 18 additional States reported type B influenza; it was widespread only in States in the central part of the country. Unlike Hong Kong strain A2 influenza, which affected all age groups, type B influenza illness occurred primarily in school-age children.

INFLUENZA VIRUS VACCINES

The Division of Biologics Standards, National Institutes of Health, regularly reviews influenza vaccine formulation, and, when indicated, recommends revision to include contemporary antigens. After characterization of the A2 Hong Kong virus in September 1968, a monovalent vaccine incorporating the new strain was recommended.

While some influenza vaccines have achieved 60 percent or greater effectiveness in protection against the same or closely related virus strains, vaccines in general civilian use often have not been this effective. Final data on vaccine field trials conducted in the 1968-69 influenza season are being compiled. Preliminary data indicate the monovalent Hong Kong strain vaccine was considerably less effective than would have been desirable.

For 1969-70, both standard and highly purified bivalent influenza vaccines will be available. The recommended adult dose will contain 400 chick cell agglutinating (CCA) units of Hong Kong strain antigen (A2/Aichi/2/68) and 300 CCA units of type B antigen (B/Mass/3/66). The highly purified vaccine is equivalent in potency to the standard vaccine but contains less nonviral protein.

VACCINE USAGE

General Recommendations

It is unlikely that there will be more than sporadic cases of influenza due to A2 strains in the 1969-70 season. Type B influenza may appear in areas where it did not occur in 1968-69.

Until good protection is provided consistently by influenza vaccine, it is not recommended for healthy adults and children.

Acknowledging its limited effectiveness, vaccine should be considered only for persons of any age with certain chronic debilitating conditions: 1) rheumatic heart disease, especially mitral stenosis; 2) such cardiovascular disorders as arteriosclerotic heart disease and hypertension, particularly with evidence of cardiac insufficiency; 3) chronic bronchopulmonary diseases, such as asthma, chronic bronchitis, cystic fibrosis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema, and advanced pulmonary tuberculosis; or 4) diabetes mellitus or Addison's disease.

Although the indications of vaccination are less clear, older persons, who may have incipient or potential chronic disease, particularly cardiovascular and bronchopulmonary, should also be considered candidates for vaccination.

Schedule

The primary series consists of two doses administered subcutaneously, preferably 6 to 8 weeks apart. (Dose volume for adults and children is specified in the manufacturers' labeling.) Persons at high risk who regularly receive influenza vaccines and had one or more doses of the monovalent vaccine containing Hong Kong strain antigen in the 1968-69 season require only a single full dose booster of bivalent vaccine. Immunization should be scheduled for completion by early December.

Local or mild systemic reactions to standard influenza vaccines are common. They occur in up to 50 percent of adults and appear to be related primarily to the non-viral components of the vaccine.

Individuals who should receive influenza vaccine but have had severe local or systemic reactions to the standard vaccine might be given a highly purified vaccine subcutaneously.

Precautions

Influenza vaccine should not be administered to anyone who is clearly hypersensitive to eggs because the vaccine viruses are grown in embryonated chicken eggs.

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MEASLES VACCINES

INTRODUCTION

Highly effective, safe vaccines are available for eliminating measles in the United States. Collaborative efforts of professional and voluntary medical and public health organizations in vaccination programs have brought a 95 percent reduction in the incidence of measles, but a continuing effort to immunize all susceptibles in the childhood population is necessary if the goal of measles eradication is to be realized.

Measles is often a severe disease, frequently accompanied by complications such as bronchopneumonia, middle ear infection, and encephalitis. Encephalitis, which follows measles in approximately one of every 1,000 cases, often causes permanent brain damage and mental retardation. One in every 10,000 measles cases is fatal.

MEASLES VIRUS VACCINES

Live, attenuated measles virus vaccines*, the original Edmonston B and the further attenuated strains (Schwarz and Moraten), are widely used in the United States. Edmonston B strains are prepared in either chick embryo or canine renal cell culture; the further attenuated strains are prepared only in chick embryo cell culture.

These measles virus vaccines produce a mild or inapparent, non-communicable infection. Fifteen percent of children receiving either the Edmonston B strain with Measles Immune Globulin (MIG) or the further attenuated strains experience fever, with temperatures of 103°F. (rectal) or higher, beginning about the sixth day after vaccination and lasting up to 5 days. About twice as many (30 percent) of those receiving Edmonston B without MIG have similar febrile responses. The great majority of reports indicate that even children with high fevers experience relatively little discomfort and minimal toxicity. As a result, febrile reactions often go unnoticed by the parents.

An antibody response develops in virtually all susceptible children given live measles virus vaccine. Edmonston B vaccine administered without MIG induces antibody at about the level of natural measles infection. Antibody titers in response to Edmonston B with MIG or to further attenuated vaccine are slightly lower. However, all of these vaccines appear to confer durable protection in most individuals.

Experience with more than 35 million vaccinations in the United States by mid-1969 indicates that live measles virus vaccines are among the safest immunizing agents available. Reports of reactions to measles vaccination have been rare, and in no case has it been shown that the reaction was actually vaccine induced and not merely temporally associated.

VACCINE USAGE

General Recommendations

All susceptible children – those who have not had natural measles or measles vaccine – should be vaccinated. It is particularly important to vaccinate susceptibles entering nursery school, kindergarten, or elementary school. They are often responsible for transmitting measles to other children in the community. In order to achieve adequate measles protection, communities should encourage ongoing programs to vaccinate all children at about 1 year of age.

The risk of acquiring measles in the United States has been greatly reduced by extensive vaccination, and susceptible children are therefore unlikely to be infected. The risk in other countries may be considerably greater; therefore, it would be wise to immunize susceptible children before they travel abroad.

Dose: The single dose of live measles vaccine should be given subcutaneously. No booster dose is needed.

Administration of the Edmonston B strain should ordinarily be accompanied by MIG 0.01 ml/lb, given with a different syringe at a different site. MIG should not be given with further attenuated measles vaccine.

Age: For maximum efficacy, measles virus vaccine should be administered when children are at least 12

*The official name of the product in use is Measles Virus Vaccine, Live, Attenuated.

months old. It may be given to infants at 9 to 12 months of age recognizing that the proportion of seroconversions may be slightly reduced. The proportion is further decreased if MIG is administered with vaccine.

Vaccination of adults at the present time is rarely necessary, because nearly all Americans over 15 years old now are immune. Limited data indicate that reactions to vaccine are no more common in adults than in children.

High risk groups: Immunization against measles is particularly important for children with chronic illnesses, such as heart disease, cystic fibrosis, and chronic pulmonary diseases, for malnourished children, and for those in institutions.

Use of Vaccine Following Exposure

Live, attenuated measles virus vaccine can usually prevent disease if administered **before or on the day of exposure** to natural measles; study findings indicate that protection is not conferred when vaccine is administered after the day of exposure. No untoward effects have been observed when vaccination followed exposure to natural measles.

Precautions

Severe febrile illnesses: Vaccination should be postponed until the patient has recovered.

Tuberculosis: Exacerbations of tuberculosis known to follow natural measles infection might, by analogy, be associated with the live, attenuated measles virus. Therefore, an individual with known active tuberculosis should be under treatment when given measles vaccine.

Although tuberculin skin testing is desirable as part of ideal health care, it need not be a routine prerequisite in community measles immunization programs. The value of protection against natural measles outweighs the theoretical hazard of possible exacerbation of an unsuspected tuberculosis infection by vaccination.

Recent Immune Serum Globulin administration: After administration of Immune Serum Globulin, vaccination should be deferred for 3 months. Persistence of measles antibody from the globulin might interfere with suitable response to the vaccine.

Marked hypersensitivity to vaccine components: Measles vaccine produced in chick embryo cell culture should theoretically not be given to children clearly hypersensitive to chicken eggs. Similarly, vaccine produced in canine renal cell culture should not be administered to children highly sensitive to dog hair or dander. To date, however, there have been no documented reports of serious or anaphylactic hypersensitivity reactions to measles vaccine in the United States.

Contraindications

Altered immune states: Administration of measles virus vaccine to children with leukemia has occasionally been followed by such serious complications as fatal giant cell pneumonia. Theoretically, attenuated measles virus infection might be potentiated by severe underlying diseases, such as lymphomas and generalized malignancies, or by lowered resistance, such as from therapy with steroids, alkylating drugs, antimetabolites, or radiation; therefore, vaccination of such patients should be avoided.

Pregnancy: On theoretical grounds, it would be reasonable to avoid vaccinating pregnant women with live, attenuated measles virus vaccine.

Management of Patients with Contraindications

If immediate protection against measles is required for persons for whom live, attenuated measles virus vaccine is contraindicated, passive immunization with MIG (dose approximately 0.1 ml/lb or 0.25 ml/kg) should be given as soon as possible after a known exposure. It is important to note, however, that this dose of MIG which is effective in preventing measles in normal children may not be equally effective in children with acute leukemia. To decrease the risk of measles infection for such children, all their close contacts who are susceptible to measles should be immunized.

Prior Immunization with Inactivated Measles Virus Vaccine

Atypical measles, sometimes severe, has occasionally followed exposure to natural measles in children previously inoculated with inactivated measles virus vaccines.

Untoward local reactions such as induration and edema have at times been observed when live measles virus vaccine was administered to persons who had previously received inactivated vaccine. Despite the risk of local reaction, children who have previously been given inactivated vaccine should also be given the live vaccine for full and lasting protection against natural infection.

SIMULTANEOUS ADMINISTRATION OF LIVE VIRUS VACCINES

There are obvious practical advantages to administering two or more live virus vaccines simultaneously. Data from specific investigations are not yet sufficient to develop comprehensive recommendations on simultaneous use, but a summary of current experience, attitudes, and practices provides useful guidance.

It has been generally recommended that live virus vaccines be given at least a month apart whenever possible – the rationale for this being that more frequent and severe adverse reactions as well as lower antibody responses otherwise might result. Field observations indicate, however, that with simultaneous administration of certain live virus vaccines, results of this kind have been minimal or absent. (For example, the third dose of trivalent oral polio-virus vaccine, which is recommended during the second year of life, is commonly given at the same time as smallpox vaccination without evident disadvantage.)

If the theoretically desirable 1-month interval is not feasible, as with the threat of concurrent exposures or disruption of immunization programs, the vaccines should preferably be given on the same day – at different sites for parenteral products. An interval of about

2 days to 2 weeks should be avoided because interference between the vaccine viruses is most likely then.

COMMUNITY IMMUNIZATION PROGRAMS

Ongoing Programs

Universal immunization as part of good health care should be accomplished through routine and intensive programs carried out in physicians' offices and public health clinics. Programs aimed at immunizing children at about 1 year of age against measles should be established by all communities. In addition, all susceptible children entering nursery school, kindergarten, and elementary school should receive vaccine because of their role in community spread of natural measles.

Special Intensive Programs

Community-wide immunization programs have been useful in the rapid distribution of live measles virus vaccine. Attention should now be directed toward systematic programs for groups of susceptible children remaining in both urban and rural areas.

Control of Measles Epidemics

Studies have shown that community-wide measles epidemics can be controlled by prompt administration of measles vaccine to **selected** groups of children, particularly the susceptibles in nursery schools, kindergartens, and the first two or three grades of elementary school. However, once measles is widely disseminated in a community, it may be necessary to immunize susceptible children **of all ages** to alter the course of the epidemic.

CONTINUED SURVEILLANCE

Continued careful surveillance of measles and its complications is necessary to appraise nationally and locally the effectiveness of measles immunization programs, particularly efforts at measles eradication. Surveillance can delineate failures to achieve adequate levels of protection and define groups in need of control programs.

Although more than 35 million doses of measles virus vaccine have now been administered in the United States, continuous and careful review of any adverse reaction remains important. All serious reactions or suspected measles illnesses in vaccinated children should be carefully evaluated and reported in detail to local and State health officials.

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MUMPS VACCINE

INTRODUCTION

Mumps, one of the common communicable diseases, is observed with greatest frequency in young school-age children. However, approximately 15 percent of reported cases occur after the onset of puberty.

Overt evidence of central nervous system disease with sequelae is rare in mumps, although meningeal involvement appears to be common. Orchitis has been reported in up to 20 percent of clinical cases occurring in postpubertal males. Symptomatic involvement of other glands and organs is observed less frequently. Nerve deafness is a very rare, but serious, complication of mumps.

All naturally acquired mumps infections, including the estimated 30 percent which are subclinical, confer durable immunity.

LIVE MUMPS VIRUS VACCINE*

Live mumps vaccine is prepared in chick embryo cell culture. It produces an inapparent, non-communicable infection following administration. Since its introduction approximately 1 year ago, mumps vaccine has been given to more than 1 million persons without report of significant side reactions clearly attributable to vaccination.

More than 95 percent of susceptible vaccinees develop detectable antibodies after vaccination. Although titers are lower than those induced by natural infection, the pattern of antibody persistence parallels

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*Official name: Mumps Virus Vaccine, Live

that seen following clinical mumps. The long-term duration of vaccine-induced immunity is unknown, but 3-year observations show continuing protection against natural infections and, in two small groups of children, antibody levels which are persisting without decline.

VACCINE USAGE

General Recommendations

Age: Live mumps vaccine may be used at any age from 12 months. It should not be administered to children less than 12 months old because of possible persistence of interfering maternal antibody. The vaccine is of particular value in children approaching puberty, adolescents, and adults, especially males, who have not had mumps parotitis, either unilateral or bilateral.**

Since the Committee's initial statement on live, attenuated mumps vaccine in 1967, further experience with the vaccine has been accumulated. In view of evidence showing continued vaccine efficacy and safety, the Committee has modified its recommendation for limited vaccination of young children and now suggests that consideration be given to immunizing all susceptible children over 1 year of age. The Committee reaffirms its position, however, that mumps vaccination programs should not be allowed to take priority over essential ongoing health activities.

Dose: A single dose of vaccine should be administered subcutaneously in the volume specified by the manufacturer.

Use of Vaccine Following Exposure

It is not known whether live mumps vaccine will provide protection when administered after exposure. There is, however, no contraindication to its use at that time.†

Precautions

Severe febrile illnesses: Vaccination should be postponed until the patient is completely recovered.

Marked hypersensitivity to vaccine components: Mumps vaccine is produced in chick embryo cell culture and should not be given to persons hypersensitive to ingested egg proteins. Also, the vaccine contains small amounts of neomycin, so it should not be given to individuals known to be sensitive to this antibiotic.

Altered immune states: Mumps vaccine virus infection might be potentiated by severe underlying diseases, such as leukemia, lymphoma, or generalized malignancy, and by lowered resistance, such as from therapy with steroids, alkylating drugs, antimetabolites, or radiation; therefore, vaccination of such patients should be avoided.

Pregnancy: On theoretical grounds, it is reasonable to avoid using live mumps vaccine during pregnancy.

Simultaneous Administration of Live Mumps Virus Vaccine with Other Live Virus Vaccines

In order to evaluate the live mumps vaccine adequately, its simultaneous administration with other vaccines should be deferred until results of controlled clinical investigations are available. Until then, it is recommended that mumps vaccination be separated from other immunization procedures by about one month whenever possible.

SURVEILLANCE

Careful surveillance of mumps is important. There is need to improve reporting of mumps cases and their complications, to demonstrate continuing vaccine effectiveness, and to document patterns of vaccine use.

**The mumps skin test with currently available antigens is an unreliable indicator of immunity.

† Inactivated mumps vaccine and Mumps Immune Globulin (Human) are of questionable effectiveness under these circumstances.

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PLAGUE VACCINE

INTRODUCTION

Plague is a sylvatic infection of rodents and their ectoparasites in many parts of the world. In the western United States, a few human cases occur each year following exposure to infected wild rodents. In some countries of Asia, Africa, and South America, epidemic plague results when the domestic rat population becomes infected. Currently the area of most intensive epidemic and epizootic infection is Vietnam.

PLAGUE VACCINE

Plague vaccines have been used since the late nineteenth century, but it has never been possible to measure their effectiveness precisely. Immunization with plague vaccine, however, is known to reduce the incidence and severity of disease.

The plague vaccine licensed for use in the United States is prepared from *Pasteurella pestis* grown in artificial media, inactivated with formaldehyde, and preserved in 0.5 percent phenol.

VACCINE USAGE

General Recommendations

Routine vaccination is **not** indicated for persons simply living in plague enzootic areas of the western United States or for travelers going to most of the countries reporting cases.* Selective immunization is advisable for the following:

1. All persons traveling to Vietnam, Cambodia, and Laos.
2. All persons whose vocations or field work brings them into frequent and regular contact with wild rodents in plague enzootic areas of the western United States, South America, Africa, or Asia.
3. All laboratory personnel working with the *P. pestis* organism or with plague-infected rodents.

Primary Immunization

All injections should be given intramuscularly.

Adults and children over 10 years old: The primary series consists of three doses of vaccine. The first two doses, 0.5 ml each, should be administered 4 or more weeks apart, followed by a third dose, 0.2 ml, 4 to 12 weeks after the second injection. When less time is available, satisfactory but less than optimal results can be obtained with two 0.5 ml injections administered at least 3 weeks apart.

Children less than 10 years old: The primary series also is three doses of vaccine, but the doses are smaller. The manufacturer's guide to proportions of the adult dose for children is: Infants under 1 year – one-fifth adult dose; 1-4 years – two-fifths adult dose; 5-10 years – three-fifths adult dose. The intervals between injections are the same as for adults.

*For a current listing, consult the most recent issue of the World Health Organization's *Weekly Epidemiological Record*

Booster Doses

Boosters should be given every 6 to 12 months while individuals remain in an area where the risk of exposure persists. Satisfactory doses for children and adults are the same volumes suggested for the third dose in the primary series. The primary series need never be repeated for booster doses to be effective.

Summary

The following table summarizes the recommended doses for primary and booster vaccination:

Dose Number	Age (Years) Under 1	1–4	5–10	Over 10
1 & 2	0.1 ml	0.2 ml	0.3 ml	0.5 ml
3 & Boosters	0.04 ml	0.08 ml	0.12 ml	0.2 ml

Reactions

Mild reactions consisting of pain, reddening, and swelling at the injection site are frequently recognized. With repeated doses, systemic reactions of fever, headache, and malaise occur more often and tend to become more pronounced. Sterile abscesses are reported to occur rarely. No fatal or disabling complications have been observed.

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POLIOMYELITIS VACCINES

INTRODUCTION

Widespread use of poliovirus vaccines since 1955 has resulted in the virtual elimination of paralytic poliomyelitis in the United States. To ensure continued freedom from the disease, it is necessary to pursue regular immunization of all children from early infancy.

Paralytic poliomyelitis declined from 18,308 cases in 1954 to 40 cases in 1967 and 48 cases in 1968. A national survey in 1968 showed that 82 percent of individuals 1-19 years old had received at least three doses of oral poliovirus vaccine (OPV)*, inactivated poliovirus vaccine (IPV)**, or both.

Nevertheless, low immunization rates still prevail in certain disadvantaged urban and rural groups, particularly for infants and young children born since the mass immunization campaigns conducted between 1958 and 1962. Most of the cases of paralytic poliomyelitis in recent years occurred in these populations.

With widespread use of poliovirus vaccine, laboratory surveillance of enteroviruses indicates that circulation of wild polioviruses has diminished markedly. It can be assumed that inapparent infections with wild strains will no longer contribute significantly to maintaining immunity; therefore, it is essential not only to continue active immunization programs for infants and children but also to make special efforts to raise the low immunization rates existing in certain other segments of the population. Population groups requiring immunization can be identified by immunization history and serologic survey.

POLIOVIRUS VACCINES

Between 1955, when IPV was introduced, and 1962, when live, attenuated vaccines became widely used, more than 400 million doses of IPV were distributed in the United States. Primary immunization with IPV plus regular booster doses provided a high degree of protection against paralytic disease.

OPV has largely replaced IPV in this country because it is easier to administer, requires no boosters, and produces an immune response like that induced by natural poliovirus infection.

Monovalent OPV types 1, 2, and 3 were widely used in the United States beginning in 1961, but they have generally been supplanted by trivalent OPV because of greater simplicity in scheduling and recordkeeping.

A primary series of three adequately spaced doses of trivalent OPV will produce an immune response to the three poliovirus types in well over 90 percent of recipients.

Very rarely, paralysis has occurred in recipients of OPV or in their close contacts within 2 months of vaccine administration. Currently, for each 9 million doses of OPV given, no more than one case of "vaccine associated" paralysis in recipients and two in recipient contacts are reported.

VACCINE USAGE

Trivalent OPV—Primary Immunization

Infants: The three-dose immunization series should be started at 6 to 12 weeks of age, commonly with the first dose of DTP. The second dose should be given not less than 6 and preferably 8 weeks later. The third dose is an integral part of primary immunization and should be administered 8 to 12 months after the second dose.

Children and adolescents: For unimmunized children and adolescents through high school age, the primary series is three doses. The first two should be given 6 to 8 weeks apart, and the third, 8 to 12 months after the second. If circumstances do not permit the optimal interval between the second and third doses, the third may be given as early as 6 weeks after the second.

Adults: Routine poliomyelitis immunization for adults residing in the continental United States is not necessary because of the extreme unlikelihood of exposure. However, an unimmunized adult at increased risk through contact with a known case or travel to areas where polio is epidemic or occurs regularly should receive trivalent OPV as indicated for children and adolescents. Persons employed in hospitals, medical laboratories, and sanitation facilities might also be at increased risk, especially if poliomyelitis is occurring in the area.

Pregnancy is not an indication for vaccine administration, nor is it a contraindication when protection is required.

Monovalent OPV—Primary Immunization

An alternative primary immunization is one dose of each of the three types of monovalent OPV given at 6 to 8 week intervals, with a dose of trivalent OPV given 8 to 12 months after the third dose of monovalent OPV to ensure adequate responses.

OPV—Booster Doses

Entering school: On entering kindergarten or first grade, all children who have completed the primary series of OPV should be given a single dose of trivalent OPV; others should complete the primary series.

There is no indication for routine booster doses of OPV beyond that given at the time of entering school.

Increased risk: A single dose of trivalent OPV can be administered to anyone who has completed the full primary series because of travel or occupational hazard as described above. The need for such an additional dose has not been established, but if there is uncertainty about the adequacy of existing protection, a single dose of trivalent OPV should be given.

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* Official names of the products in use: (1) Poliovirus Vaccine, Live Oral, Type 1, (2) Poliovirus Vaccine, Live, Oral, Type 2, (3) Poliovirus Vaccine, Live Oral, Type 3, (4) Poliovirus Vaccine, Live, Oral Trivalent.

** Official name: Poliomyelitis Vaccine.

Contraindications

Altered immune states: Infection with live, attenuated polioviruses might be potentiated by severe underlying diseases, such as leukemia, lymphoma, or generalized malignancy, or by lowered resistance, such as from therapy with steroids, alkylating drugs, antimetabolites, or radiation; therefore, vaccination of such patients should be avoided.

IPV—Primary Immunization

All ages: Four parenteral doses should be given, three at approximately 1-month intervals and the fourth 6 to 12 months after the third. This schedule can be integrated with DTP immunization beginning at 6 to 12 weeks of age.

IPV—Booster Doses

A booster dose every 2 to 3 years is generally recommended to ensure adequate levels of antibody. The need for IPV boosters could be obviated by a full course of OPV. For individuals at particular risk, as described previously, at least one dose of trivalent OPV, but preferably a full primary series, is recommended.

EPIDEMIC CONTROL

For operational purposes in the United States, an "epidemic" of poliomyelitis is defined as two or more cases caused by the same poliovirus type and occurring within a 4-week period in a circumscribed population, such as that of a city, county, or a metropolitan area. An epidemic can be controlled with either trivalent OPV, or, after identification of the responsible type of poliovirus, homotypic monovalent OPV. Within the epidemic area, all persons over 6 weeks of age who have not been completely immunized or whose immunization status is unknown should promptly receive OPV.

SIMULTANEOUS ADMINISTRATION OF LIVE VIRUS VACCINES

There are obvious practical advantages to administering two or more live virus vaccines simultaneously. Data from specific investigations are not yet sufficient to develop comprehensive recommendations on simultaneous use, but a summary of current experience, attitudes, and practices provides useful guidance.

It has been generally recommended that live virus vaccines be given at least 1 month apart whenever possible – the rationale for this being that more frequent and severe adverse reactions as well as diminished antibody responses otherwise might result. Field observations indicate, however, that with simultaneous administration of certain live virus vaccines, results of this type have been minimal or absent. (For example, the third dose of trivalent oral poliovirus vaccine, which is recommended during the second year of life, is commonly given at the same time as smallpox vaccination without evident disadvantage.)

If the theoretically desirable 1-month interval is not feasible, as with the threat of concurrent exposures or disruption of immunization programs, the vaccines should preferably be given on the same day – at different sites for parenteral products. An interval of about 2 days to 2 weeks should be avoided because interference between the vaccine viruses is most likely then.

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RABIES PROPHYLAXIS

INTRODUCTION

Although cases of rabies in humans are rare in the United States, thousands of persons receive rabies prophylaxis each year. The following approach to prevention is based on a contemporary interpretation of both the risk of infection and the efficacy of treatment and incorporates the basic concepts of the WHO Expert Committee on Rabies.

The problem of whether or not to immunize those bitten or scratched by animals suspected of being rabid is a perplexing one for physicians. All available methods of systemic treatment are complicated by numerous instances of adverse reactions, a few of which have resulted in death or permanent disability. Furthermore, the decision must be made immediately, because the longer treatment is postponed, the less likely it is to be effective.

Accepted evidence of the efficacy of active and of passive immunization after exposure was derived largely from experimental studies in animals. Because rabies has on occasion developed in humans who had received antirabies prophylaxis, its value has been questioned. Evidence from laboratory and field experience in many areas of the world, however, indicates that post-exposure prophylaxis is usually effective when appropriately used.

Rabies in the United States

Rabies in humans has decreased from an average of 22 cases per year in 1946-1950, to only one or two cases per year since 1963. Rabies in domestic animals has diminished similarly. In 1946, for example, there were more than 8,000 cases of rabies in dogs, compared with 296 in 1968. Thus, the likelihood of humans' being exposed to rabies by domestic animals has decreased greatly, although bites by dogs and cats continue to be responsible for the overwhelming majority of antirabies treatments.

In contrast, the disease in wildlife – especially skunks, foxes, and bats – has become increasingly prominent in recent years, accounting for more than 70 percent of all reported cases of animal rabies in 1968. Wild animals constitute the most important source of infection for man and domestic animals in the United States today. In 1968, only three States reported no wildlife rabies.

Antirabies Treatment in the United States

More than 30,000 persons receive post-exposure antirabies treatment each year. However, there is no information on the number of persons actually exposed to rabid animals.

In the United States, nervous tissue origin rabies vaccine of the Semple type (NTV) was used almost exclusively until 1957, when duck embryo origin vaccine (DEV) was licensed. More than 90 percent of those who received rabies prophylaxis in the United States in 1968 were given DEV.

RABIES VACCINES

Duck Embryo Vaccine (DEV)

Prepared from embryonated duck eggs infected with a fixed virus and inactivated with beta-propiolactone.

Nervous Tissue Vaccine (NTV)

Prepared from rabbit brain infected with a fixed virus and inactivated with phenol (Semple type) or inactivated with ultraviolet irradiation.

Antigenicity of Vaccines

The antigenicity of NTV is often higher than that of DEV when tested in experimental animals. However, all lots of both vaccines must pass minimum potency tests established by the Division of Biologics Standards, National Institutes of Health. There is evidence that the serum antibody response in humans is detectable sooner with DEV, but the eventual level of response is frequently higher with NTV.

Effectiveness of Vaccines in Humans

In the United States, comparative effectiveness of vaccines can be judged only by reported failures. During the years 1957 through 1968 when both vaccines were available, there were six rabies deaths among the 125,000 NTV-treated persons (1:20,800) and eight among the 225,000 treated with DEV (1:28,100).

Reactions

Erythema, pruritis, pain, and tenderness at the site of inoculation are common with both DEV and NTV. Systemic responses including low-grade fever, or rarely shock, may occasionally occur late in the course of therapy with either vaccine, usually after five to eight doses. In rare instances, serious reactions have occurred after the first dose of DEV or NTV, particularly in persons previously sensitized with vaccines containing avian or rabbit brain tissue.

As described previously, neuroparalytic reactions occur rarely with DEV. They much more frequently follow NTV, especially after repeated courses of treatment with this preparation.

Choice of Vaccine

Treatment-failure rates for the two vaccines are not significantly different; therefore, the lower incidence of central nervous system reaction with DEV makes it preferable to NTV.

RATIONALE OF TREATMENT

EVERY EXPOSURE TO POSSIBLE RABIES INFECTION MUST BE INDIVIDUALLY EVALUATED.

In the United States, the following factors should be considered before specific antirabies treatment is initiated:

Species of Biting Animal

Carnivorous animals (especially skunks, foxes, coyotes, raccoons, dogs, and cats) and bats are more likely to be infective than other animals. Bites of

rodents, including squirrels, chipmunks, rats, and mice, seldom, if ever, call for specific rabies prophylaxis.

Circumstances of Biting Incident

An UNPROVOKED attack is more likely to mean that the animal is rabid. (Bites during attempts to feed or handle an apparently healthy animal should generally be regarded as PROVOKED.)

Extent and Location of Bite Wound

The likelihood that rabies will result from a bite varies with its extent and location. For convenience in approaching management, two categories of exposure are widely accepted:

Severe: Multiple or deep puncture wounds, or any bites on the head, face, neck, hands, or fingers.

Mild: Scratches, lacerations, or single bites on areas of the body other than the head, face, neck, hands, or fingers. Open wounds, such as abrasions, suspected of being contaminated with saliva also belong in this category.

Vaccination Status of Biting Animal

An adult animal immunized properly with one or more doses of rabies vaccine has only a minimal chance of developing rabies and transmitting the virus.

Presence of Rabies in Region

If adequate laboratory and field records indicate that there is no rabies infection in a domestic species within a given region, local health officials may be justified in taking this into consideration in making recommendations on antirabies treatment following a bite by that species.

MANAGEMENT OF BITING ANIMALS

A dog or cat that bites a person should be captured, confined, and observed by a veterinarian for at least 5 days, preferably 7 to 10. Any illness in the animal should be reported immediately to the local health department. If the animal dies, the head should be removed and shipped under refrigeration to a qualified laboratory for examination. Clinical signs of rabies in wild animals cannot be interpreted reliably; therefore, any wild animal that bites or scratches a person should be killed at once (without unnecessary damage to the head) and the brain examined for evidence of rabies.

LOCAL TREATMENT OF WOUNDS

IMMEDIATE and thorough local treatment of all bite wounds and scratches is perhaps the most effective means of preventing rabies. Experimentally, the incidence of rabies in animals can be markedly reduced by local therapy alone.

First-Aid Treatment to be Carried out Immediately

Copious flushing with water, soap and water, or detergent and water.

Treatment by or Under Direction of Physician

1. Thorough flushing and cleansing into the wound with soap solution. Quaternary ammonium compounds may also be used.*

2. If antirabies serum is indicated, (See Passive Immunization), some of the total dose should be thoroughly infiltrated around the wound. As in all instances when horse serum is to be used, a careful history should be taken and prior tests for hypersensitivity performed.

3. Tetanus prophylaxis and measures to control bacterial infection, as indicated.

POST-EXPOSURE PROPHYLAXIS

Active Immunization

Primary immunization: At least 14 daily injections of vaccine in the dose recommended by the manufacturer. They should be given subcutaneously in the abdomen, lower back, or lateral aspect of thighs; rotation of sites is recommended.

For severe exposure, 21 doses of vaccine are recommended. These may be given as 21 daily doses or 14 doses in the first 7 days (either as two separate injections or a double dose), and then seven daily doses.

Booster doses: Two booster doses, one 10 days and the other at least 20 days after completion of the primary course. The two booster doses are particularly important if antirabies serum was used in the initial therapy.

Precautions: When rabies vaccine must be given to a person with a history of hypersensitivity, especially to avian or rabbit tissues, antihistaminic drugs should be given. Epinephrine is helpful in reactions of the anaphylactoid type. If serious allergic manifestations preclude continuation of prophylaxis with one vaccine, the other may be used.

When meningeal or neuroparalytic reactions develop, vaccine treatment should be discontinued altogether. Corticotrophin or corticosteroids are used for such complications.

Passive Immunization

Hyperimmune serum has proved effective in preventing rabies. Its use in combination with vaccine is considered the best post-exposure prophylaxis. However, the only preparation of antirabies serum now available in the United States is of equine origin. Because horse serum has induced serum sickness in at least 20 percent of those who have received it, it should be used only when indicated.

Hyperimmune serum is recommended for most exposures classified as severe, and for ALL BITES by rabid animals and UNPROVOKED BITES by wild carnivores

*All traces of soap should be removed before applying quaternary ammonium compounds because soap neutralizes their activity.

ANIMAL BITE TREATMENT CHECKLIST

(See text for Details)

1	2	3	4
FLUSH WOUND IMMEDIATELY (FIRST AID)	CLEANSE WOUND THOROUGHLY UNDER MEDICAL SUPERVISION	ANTIRABIES SERUM and/or VACCINE AS INDICATED	TETANUS PROPHYLAXIS & ANTIBACTERIAL WHEN REQUIRED

POST-EXPOSURE ANTIRABIES PROPHYLAXIS GUIDE

THE FOLLOWING RECOMMENDATIONS ARE INTENDED ONLY AS A GUIDE. THEY MAY BE MODIFIED ACCORDING TO KNOWLEDGE OF THE SPECIES OF BITING ANIMAL AND CIRCUMSTANCES SURROUNDING THE BITING INCIDENT. (See text for details.)

ANIMAL BITE		TREATMENT		
SPECIES	STATUS AT TIME OF ATTACK	EXPOSURE		
		NO LESION	MILD*	SEVERE*
DOG CAT	healthy	none	none [1]	S [1]
	signs suggestive of rabies	none	V [2]	S+V [2]
	escaped or unknown	none	V	S+V
	rabid	none	S+V	S+V
SKUNK FOX RACCOON COYOTE BAT	REGARD AS RABID IN unprovoked attack	none	S+V	S+V
OTHER	consider individually—see Rationale of Treatment in text			

Code: * = See definitians in text.
V = Rabies Vaccine.
S = Antirabies Serum.
1 = Begin vaccine at first sign af rabies in biting dag ar cat during holding periad (preferably 7 - 10 days).
2 = Discantinue vaccine if biting dag ar cat is healthy 5 days after expasure, ar if acceptable labaratory negativity has been demanstrated in animal killed at time af attack. If abserved animal dies after 5 days and brain is pasitive, resume treatment.

and bats. When indicated, antirabies serum should be used regardless of the interval between exposure and treatment.

The dose recommended is 1,000 units (one vial) per 40 pounds of body weight. A portion of the antiserum should be used to infiltrate the wound, and the rest administered intramuscularly. As previously noted, a careful history must be obtained and appropriate tests for hypersensitivity performed.*

PRE-EXPOSURE PROPHYLAXIS

The relatively low frequency of reactions to DEV has made it more practical to offer pre-exposure immunization to persons in high-risk groups: veterinarians, animal handlers, certain laboratory workers, and individuals, especially children, living in areas of the world where rabies is a constant threat. Others whose vocational or avocational pursuits result in frequent contact with dogs, cats, foxes, skunks, or bats should also be considered for pre-exposure prophylaxis.

Two 1.0 ml injections of DEV given subcutaneously in the deltoid area 1 month apart should be followed by a third dose 6 to 7 months after the second dose. This series of three injections can be expected to have produced neutralizing antibody in 80 to 90 percent of vaccinees by 1 month after the third dose.

For more rapid immunization, three 1.0 ml injections of DEV should be given at weekly intervals with a fourth dose 3 months later. This schedule elicits an antibody response in about 80 percent of the vaccinees.

All who receive the pre-exposure vaccination should have their serum tested for neutralizing antibody 3 to 4 weeks after the last injection. Tests for rabies antibody can be arranged with or through State health department laboratories. If no antibody is detected, booster doses should be given until a response is demonstrated. Persons with continuing exposure should receive 1.0 ml boosters every 2 to 3 years.

*A guide for use of animal serum is included in the recommendation for tetanus prophylaxis in wound management prepared by the PHS Advisory Committee on Immunization Practices.

When an immunized individual with previously demonstrated antibody is exposed to rabies, it is suggested that for a mild exposure, one booster dose of vaccine be given, and for a severe exposure, five daily doses of vaccine plus a booster dose 20 days later. If it is not known whether an exposed person had antibody, the complete post-exposure antirabies treatment should be given.

ACCIDENTAL INOCULATION WITH LIVE RABIES VIRUS VACCINE

Persons inadvertently inoculated with attenuated rabies vaccines for use in animals, such as the Flury strain vaccine, are not considered at risk, and antirabies prophylaxis is not indicated.

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RUBELLA VIRUS VACCINE PRELICENSING STATEMENT †

INTRODUCTION

The live, attenuated rubella virus vaccine* soon to become available appears to be a highly effective immunizing agent and the first suitable method of controlling rubella.

Rubella is generally a mild illness, but if the infection is acquired by a woman in the early months of pregnancy, it poses a direct hazard to the fetus. Preventing infection of the fetus is the principal objective of rubella control. This can best be achieved by eliminating the transmission of virus among children, who are the major source of infection for susceptible pregnant women. Furthermore, the live, attenuated rubella virus vaccine is safe and protective for children, but not for pregnant women because of an undetermined risk of the vaccine virus for the fetus.

Rubella

Rubella is one of the common childhood exanthems. Most cases occur in school-age children particularly during the winter and spring. By early adulthood, approximately 80 to 90 percent of individuals in the United States have serological evidence of immunity.

Rubella is clinically variable, and its common features, such as post-auricular and sub-occipital lymphadenopathy and transient erythematous rash, are often overlooked or misdiagnosed. A mild febrile illness may not be recognizable as rubella, and moreover, subclinical infection occurs, which further decreases the reliability of clinical history.

Complications of rubella are rare in children, but in adults, particularly women, the illness is commonly accompanied by transient polyarthritis. Far more important is the frequent occurrence of fetal abnormalities when a woman acquires rubella in the first trimester of pregnancy.

Rubella Immunity

Immunity following rubella appears to be long lasting, even after mild illness or clinically inapparent infection. The only reliable evidence of immunity is a positive serological test. However, because of the variation among reagents and technical procedures, results of serological tests should be accepted only from laboratories of recognized competency that regularly perform these tests.

At the present time, the hemagglutination-inhibition (HI) antibody determination is particularly useful for evaluating immunity. It is a rapid and sensitive procedure. The complement fixation (CF) and other serological tests are less useful.

LIVE RUBELLA VIRUS VACCINE

Live rubella virus vaccine is prepared in cell culture of avian or mammalian tissues. It is administered as a single subcutaneous injection. Although vaccinees shed virus from the pharynx at times for 2 or more weeks after vaccination, there is no clear evidence of communicability. Approximately 95 percent of susceptible vaccinees develop antibodies, but titers are lower than those observed following natural rubella infection. Recent investigations have shown that vaccination affords protection against illness following either natural exposure or artificial challenge.

Antibody levels have declined very little during the 3-year period of observation of children who were among the first to be immunized with rubella vaccine. Long-term protection is likely, but its exact duration can be established only by continued observation.

More than 30,000 susceptible children have received live rubella virus vaccine in field investigations, with almost no untoward reactions. Only rarely has transient arthralgia or evanescent rash been reported in children.

Many susceptible women have had lymphadenopathy, arthralgia, and transient arthritis beginning 2 to 4 weeks after vaccination; however, fever, rash, and other features of naturally acquired rubella have occurred less commonly. Not enough susceptible men have been vaccinated to show whether they experience comparable reactions as frequently as women.

VACCINE USAGE

General Recommendations

Live rubella virus vaccine is recommended for boys and girls between the age of 1 year and puberty. Vaccine should not be administered to infants less than 1 year old because of possible interference from persisting maternal rubella antibody.

Children in kindergarten and the early grades of elementary school deserve initial priority for vaccination because they are commonly the major source of virus dissemination in the community. A history of rubella illness is usually not reliable enough to exclude children from immunization.

Vaccination of adolescent or adult males is of much lower priority because so few are susceptible. However, the vaccine may be useful in preventing or controlling outbreaks of rubella in circumscribed population groups.

Pregnant women should not be given live rubella virus vaccine. It is not known to what extent infection of the fetus with attenuated virus might take place following vaccination, or whether damage to the fetus could result. Therefore, routine immunization of adolescent girls and adult women should not be undertaken because of the danger of inadvertently administering vaccine before pregnancy becomes evident.

Women of childbearing age may be considered for vaccination only when the possibility of pregnancy in

†Rubella vaccine was licensed on June 9, 1969, for distribution in the U.S.A. Revision of the ACIP recommendation awaits accumulation of data based on experience.

*Official name: Rubella Virus Vaccine, Live.

the following 2 months is essentially nil; each case must be considered individually. This cautious approach to vaccinating postpubertal females is indicated for two reasons: First, because of the theoretical risk of vaccination in pregnancy; and second, because significant congenital anomalies occur regularly in approximately 3 percent of all births, and their fortuitous appearance after vaccine had been given during pregnancy could lead to serious misinterpretation.

If vaccination of a woman of childbearing age is contemplated, the following steps are indicated:

Optimally, the woman should be tested by the HI test for susceptibility to rubella (See Rubella Immunity).

If **immune**, she should be assured that vaccination is unnecessary.

If **susceptible**, she may be vaccinated only if she understands that it is imperative for her to avoid becoming pregnant for the following 2 months. (To ensure this, a medically acceptable method for pregnancy prevention should be followed. This precaution also applies to women in the immediate postpartum period.) Additionally, she should be informed of the frequent occurrence of self-limited arthralgia and possible arthritis beginning 2 to 4 weeks after vaccination.

Use of Vaccine Following Exposure

There is no evidence that live rubella virus vaccine given after exposure will prevent illness. There is, however, no contraindication to vaccinating children already exposed to natural rubella. For women exposed to rubella, the concepts listed previously apply.

Precautions and Contraindications

Pregnancy: Live rubella virus vaccine is contraindicated. (See General Recommendations)

Altered immune states: Attenuated rubella virus infection might be potentiated by severe underlying diseases, such as leukemia, lymphoma, or generalized malignancy, and when resistance has been lowered by therapy with steroids, alkylating drugs, antimetabolites, or radiation. Vaccination of such patients should be avoided.

Severe febrile illnesses: Vaccination should be postponed until the patient has recovered.

Hypersensitivity to vaccine components: Rubella vaccine is produced in cell culture. Care should be exercised in administering vaccine to persons with known hypersensitivity to the species from which the cells were derived (indicated in the labeling). The vaccine contains a small amount of neomycin and should not be given to individuals known to be sensitive to this antibiotic.

Simultaneous Administration of Live Rubella Virus Vaccine and Other Live Virus Vaccines

Simultaneous administration of live rubella virus vaccine and other live virus vaccines should be deferred until results of controlled clinical investigations are available. Until then, it is recommended that rubella vaccination be separated by at least 1 month from administration of other live virus vaccines.

SURVEILLANCE

Careful surveillance of rubella infection is particularly important with an effective vaccine in use. Emphasis should be placed upon improved diagnosis and reporting of rubella, of the congenital rubella syndrome, and of complications of the disease. Competent laboratory investigation of all infants with birth defects suspected of being due to rubella is essential. It will likewise be important to observe patterns of vaccine use and determine their effectiveness.

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SMALLPOX VACCINE

INTRODUCTION

In the United States, protection of the population against smallpox through routine vaccination of infants and revaccination of older children and adults represents the principal mechanism of defense against the indigenous spread of the disease once introduced. This approach to community protection, as with all practices in preventive medicine, demands continuing reassessment of the potential risk of the disease in comparison with the efficacy and risk associated with preventive procedures.

THE RISK OF INTRODUCING SMALLPOX

While the current risk of introduction and subsequent transmission of smallpox in the United States is difficult to define, not one confirmed case of smallpox has occurred since 1949 despite increased travel by United States citizens and other nationals to and from smallpox endemic areas. The reservoirs of endemic smallpox in Asia, Africa, and South America are shrinking, and in these areas many of the smallpox cases are now occurring away from urban centers. Furthermore, recent evidence suggests that the communicability of smallpox through casual contact, as on common carriers, is quite small.

It must be recognized, however, that quarantine measures at ports of entry offer at best only partial protection against the introduction of smallpox. In almost half of the 39 instances since 1950, when smallpox was introduced into Western Europe, nationals of the country involved were responsible. Should smallpox be introduced into the United States, it is similarly quite possible that a United States citizen returning from abroad would introduce the disease.

Smallpox, particularly variola major, is a highly virulent disease even with excellent medical care. The mortality rate for unvaccinated persons was 40 percent in Sweden and England in the outbreaks of 1962-63.

Because few physicians in practice today have seen clinical smallpox, it is not surprising that in several recent European outbreaks the disease went unrecognized until the third generation of cases, or even later. During a 1966 outbreak of variola minor in England, the diagnosis of smallpox was not made until the fourth cycle of transmission, when 23 cases had already occurred – more than 10 weeks after the first identifiable case. Should the disease be introduced into the United States, a similar course of events could occur.

SMALLPOX VACCINE

Effectiveness

The efficacy of smallpox vaccine has never been precisely measured in controlled trials. It is, however, generally agreed that vaccination with fully potent vaccine confers a high level of protection for at least 3 years. Vaccination provides substantial but waning immunity for 10 years or more, but appears to protect against a fatal outcome of disease for an even longer period, perhaps for decades.

Complications and Risks

It is recognized that with smallpox vaccination, as with other medical procedures, there is a definite, measurable risk of untoward reaction and rarely death. Comprehensive national surveys to determine the frequency of smallpox vaccine complications in the United States were made in 1963 and 1968. In 1968, among more than 5.6 million primary vaccinees and nearly 8.6 million revaccinees and their contacts, 16 cases of encephalitis, 11 cases of vaccinia necrosum, and 126 cases of eczema vaccinatum occurred in association with vaccination. Nine persons died. A substantial number of less serious complications, some of which necessitated hospitalization, were also recorded. All deaths and virtually all complications occurred in primary vaccinees.

Survey data show clearly that more than half of the complications from smallpox vaccination would not have occurred if acknowledged contraindications to vaccination had been closely observed. Furthermore, complication rates appear to be at least twice as high for children under one year of age as for slightly older children. Also primary vaccination of adolescents and adults appears to carry a higher risk of adverse reactions than vaccination of younger children.

Thus, with no introductions of smallpox into the United States in 20 years and with a small but definite risk of adverse reactions to smallpox vaccine, the justification for its routine use must be examined regularly. In weighing the relative risks, the consequences of having to vaccinate persons for the first time as adults needing protection against smallpox when entering military service, traveling overseas, working in medical or allied health professions, or being exposed in local outbreaks must be considered.

OTHER PROPHYLACTIC AGENTS

In recent years, Vaccinia Immune Globulin (VIG) and certain antiviral compounds have been found to be effective in conferring protection against smallpox when administered shortly after exposure to the disease. At present, none appears to be a satisfactory alternative to vaccination, and more importantly, none confers more than temporary protection. Thus, unless the first introduced smallpox case could be promptly and correctly diagnosed and all contacts quickly identified and treated, interruption of subsequent transmission of the disease by using these materials would be virtually impossible.

It is of added practical importance that antiviral compounds have considerable gastrointestinal toxicity and the supply of VIG is limited. Therefore, none of these

prophylactic agents is suitable for mass use as a substitute for vaccination at the time of an actual or potential outbreak.

CONCLUSIONS AND RATIONALE FOR VACCINATION

In recent years, international travel has increased dramatically, and while the reservoir of endemic smallpox has decreased, the potential for introduction of smallpox into the United States continues.

The 1966 World Health Assembly agreed to embark on an intensive 10-year smallpox eradication program. Vaccination campaigns in many of the developing countries have been very effective, so there is every reason to anticipate success with this program. Eradication of endemic smallpox represents the most direct attack on the problem and the surest means of protecting the United States.

Until eradication is achieved or, at least, nears realization, vaccination, although not wholly without risk, now represents the only suitable approach for community protection in the United States. Comparing the risks of smallpox spread in the United States and the risk of primary vaccination complications for adults with the risks of complications of vaccination of children, it seems prudent for the present to continue the practice of regular smallpox vaccination in early childhood and subsequent periodic revaccination.

VACCINE USAGE

The following smallpox vaccination practices are recommended for the United States:*

Primary Vaccination

Age: Within the second year of life (i.e., between first and second birthdays) or at any age under conditions of exposure or foreign travel.

Revaccination

School entrance: On entering kindergarten or elementary school.

Potential exposure: At 3-year intervals for persons who conceivably might be exposed in endemic or potentially endemic areas by virtue of international travel or likely to be exposed by newly introduced infection into the United States, in particular: hospital personnel, including physicians, nurses, attendants, and laboratory and laundry workers; other medical, public health, and allied professions; and morticians and other mortuary workers.

Routine vaccination: At approximately 10-year intervals for all others.

*All persons, regardless of age, entering the United States from non-exempt areas are required to be vaccinated or revaccinated within three years unless vaccination is medically contraindicated. The International Sanitary Regulations provide that "if a vaccinator is of the opinion that vaccination is contraindicated on medical grounds, he should provide the persons with written reasons underlying that opinion, which health authorities may take into account."

Site of Vaccination

The skin over the insertion of the deltoid muscle or the posterior aspect of the arm over the triceps muscle.

Methods of Vaccination

Multiple pressure: A small drop of vaccine is placed on the dry, cleansed skin, and a series of pressures is made in an area about 1/8-inch in diameter with the side of a sharp, single pointed, sterile needle held tangentially to the skin. The pressures are made with the side of the needle. For primary vaccination, 10 pressures are adequate; for revaccination, 30 pressures should be made. (Proportionately fewer pressures are required with a "bifurcated" needle.) The remaining vaccine should be wiped off with dry, sterile gauze. Preferably, no dressing should be applied to the site.

Jet injection: The recommended dose of vaccine specifically manufactured for this purpose is injected intradermally with a jet injection apparatus. Excess vaccine should be wiped off the arm with dry, sterile gauze. Preferably, no dressing should be applied to the site.

Other techniques: Vaccination may be performed with other devices and techniques shown to be equally effective in assuring takes.

Interpretation of Responses†

Time of inspection: The vaccination site should be inspected 6 to 8 days after vaccination. The response at this time should be interpreted.

Primary vaccination: A "successful" primary vaccination shows a typical Jennerian vesicle. If none is observed, vaccination procedures should be checked and vaccination repeated with vaccine from another lot until a successful result is obtained.

Revaccination: Two types of revaccination response are defined by the WHO Expert Committee on Smallpox, eliminating use of older terms such as "accelerated" and "immune." They are:

Major reaction – A vesicular or pustular lesion or an area of definite palpable induration or congestion surrounding a central lesion which may be a crust or an ulcer. This reaction indicates that virus multiplication has taken place and that the revaccination is successful.

Equivocal reaction – All reactions other than "major reactions." They may be the consequences of immunity adequate to suppress virus multiplication or may represent only allergic reactions to an inactive vaccine. If an equivocal reaction is observed, revaccination procedures should be checked and revaccination repeated with vaccine from another lot.

Types of Smallpox Vaccine

Smallpox vaccine is available both in the glycerinated and the lyophilized form. Both forms, when properly preserved and administered, afford excellent protection. The glycerinated form requires constant refrigeration in all stages of transport and storage at temperatures

†For purposes of validating an International Certificate of Vaccination, primary vaccination must be inspected. Although desirable, inspection of revaccination is not mandatory.

recommended by the manufacturer. Comparatively minor storage difficulties may reduce its potency enough to decrease efficacy in vaccination and particularly in revaccination. Even in excellent medical facilities, the glycerinated vaccine is often stored under improper conditions. Use of the much more stable lyophilized vaccine would ensure more consistently effective vaccination. Due care must be exercised to provide proper handling of the lyophilized vaccine after reconstitution as directed by the manufacturer.

Contraindications

Skin disorders: Eczema and other forms of chronic dermatitis in the individual to be vaccinated or in a household contact. If vaccination is required for an individual with dermatitis, because of potential exposure in an endemic area, VIG should be administered to the vaccinee. If there is real need to vaccinate an individual who may thus create a hazard for a household contact with dermatitis, consideration should be given to separating the vaccinee from his contact until a crust has developed.

Pregnancy: Vaccinia virus rarely may cross the placental barrier at any stage of pregnancy and infect the fetus. Virtually all cases of fetal vaccinia have followed primary vaccination. If vaccination is indicated because of potential exposure in an endemic area, Vaccinia Immune Globulin should generally be given simultaneously with the vaccine, particularly in cases of primary vaccination. VIG will not prevent a take.

Altered immune states: Leukemia, lymphoma, and other reticuloendothelial malignancies; dysgammaglobulinemia; therapy with immunosuppressive drugs, such as steroids and antimetabolites; or radiation. If exposure should by chance occur, or if vaccination is absolutely essential, persons with any of the above conditions should be given Vaccinia Immune Globulin.

VACCINIA IMMUNE GLOBULIN

Prophylactic Use

Dose: 0.3 ml/kg by the intramuscular route.

Therapeutic Use

Dose and indications: 0.6 ml/kg by the intramuscular route. For eczema vaccinatum, vaccinia (progressive vaccinia), or autoinoculation vaccinia of the eye, VIG may be effective. For severe cases of generalized vaccinia, VIG may be helpful in treatment, but such cases almost invariably have a favorable outcome anyway. For mild cases of generalized vaccinia or autoinoculation not involving the eye, VIG is generally considered unnecessary. For postvaccinial encephalitis, VIG is of no proved value.

THIOSEMICARBAZONES

Certain of the thiosemicarbazone derivatives reportedly have a short-term protective effect against smallpox and possibly a therapeutic effect on individuals with severe vaccinial complications These are still experimental drugs and are not available for general use.

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TYPHOID VACCINE

INTRODUCTION

The incidence of typhoid fever has declined steadily in the United States in the last half century, and in the recent years fewer than 400 cases have been reported annually. The continuing downward trend is due largely to better sanitation and other control measures; vaccine is not deemed to have played a significant role.

TYPHOID VACCINES

Although typhoid vaccines have been used for many decades, only recently has definitive evidence of their effectiveness been observed in well controlled field investigations. Several different preparations of typhoid vaccine have been shown to protect 70 to 90 percent of recipients, depending in part on the degree of their subsequent exposure.

VACCINE USAGE

Routine typhoid vaccination is **no longer** recommended for persons in the United States. Selective immunization is, however, indicated in the following situations:

1. Intimate exposure to a known typhoid carrier, as would occur with continued household contact.
2. Community or institutional outbreaks of typhoid fever.
3. Foreign travel to areas where typhoid fever is endemic.

Typhoid vaccination should not be interpreted as permitting relaxation in careful selection of foods and water in areas where typhoid infections are occurring.

Although typhoid vaccine was at one time suggested for persons going to summer camps and those in areas where flooding has occurred, there are no data to support the continuation of these practices.

Primary Immunization

On the basis of the field trials referred to above, the following dosages of vaccines available in the USA are recommended:

Adults and children over 10 years old: 0.5 ml subcutaneously on two occasions, separated by 4 or more weeks.

Children less than 10 years old*: 0.25 ml subcutaneously on two occasions, separated by 4 or more weeks.

In instances where there is not sufficient time for two doses to be administered at the interval specified, it has been common practice to give three doses of the same volumes listed above at weekly intervals recognizing that this schedule may be less effective. When vaccine is to be administered for travel overseas under constraint of time, a second dose may be administered en route at a more suitable interval.

*Since febrile reactions to typhoid vaccine are common, an antipyretic may be indicated.

Booster Doses

Under conditions of continued or repeated exposure, a booster dose should be given at least every 3 years. Even when more than 3 years have elapsed since the prior immunization, a single booster injection is sufficient.

The following alternative routes and dosages of booster immunization can be expected to produce comparable antibody responses; generally less reaction follows vaccination by the intradermal route (except when acetone killed and dried vaccine is used. This vaccine should not be given intradermally).

Adults and children over 10 years old: 0.5 ml subcutaneously or 0.1 ml intradermally.

Children 6 months to 10 years*: 0.25 ml subcutaneously or 0.1 ml intradermally.

PARATYPHOID A AND B VACCINES

The effectiveness of paratyphoid A vaccine has never been established, and recent field trials have shown that available paratyphoid B vaccines are not effective, in the usually small amounts contained in "TAB" vaccines. Knowing this and recognizing that combining paratyphoid A and B antigens with typhoid vaccine increases the risk of vaccine reaction, paratyphoid A and B vaccines should not be used.

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TYPHUS VACCINE

INTRODUCTION

The United States has not experienced an outbreak of louse-borne (epidemic) typhus since 1922. The last reported case, 1950, did not result from an indigenous source of infection.

Louse-borne typhus was widespread in many countries affected by World War II. Since 1945, reported cases have declined steadily. Effective insecticides and generally improved standards of living have permitted many populations to free themselves of louse infestation. A human reservoir of latent infections persists in many parts of the world, and resurgence of the disease might occur under conditions of war or disaster. Vaccination of any civilian population in the United States, however, is unwarranted.

TYPHUS VACCINE

Typhus vaccines of the type available today were first used widely in World War II. There were no deaths from typhus among vaccinated persons during the North African campaign, and incidence of disease in the vaccinated was reportedly lower than in the unvaccinated. In unvaccinated adults, the case-fatality ratio is reported to be 20 percent or higher.

Although no controlled studies of typhus vaccine have been carried out in human populations, experience from the field and the laboratory suggests that the incidence and severity of typhus cases is diminished among the vaccinated, especially if booster doses have been received.

Typhus vaccine is prepared from formaldehyde inactivated *Rickettsia prowazekii* grown in embryonated eggs. This vaccine provides protection against only louse-borne (epidemic) typhus; it does not protect against murine or scrub typhus.

VACCINATION USAGE

Vaccination for International Travel

The rarity of epidemic typhus minimizes the need for vaccination. Typhus is at present no threat to United States residents visiting most other countries. This is true even in places still reporting large numbers of cases if travel is limited to urban areas with modern hotel accommodations. It is only in mountainous, highland, or areas where a cold climate and other local conditions favor louse infestation that a potential threat exists.

Vaccination may be indicated for travelers to rural or remote highland areas of Ethiopia, Rwanda, Burundi, Mexico, Ecuador, Bolivia, or Peru, and mountainous areas of Asia. Even there, however, the risk of typhus for U.S. travelers is extremely low. No typhus case in an American traveler is known to have occurred in recent years. Vaccination against typhus is not required by any country as a condition for entry.

Typhus vaccination is suggested only for the following special-risk groups:

1. Such persons as scientific investigators (e.g., anthropologists, archaeologists, or geologists), oil-field and construction workers, missionaries, and some government workers who live in or visit areas where the disease actually occurs and who will be in close contact with the indigenous population in such areas.

2. Medical personnel, including nurses and attendants, providing care for patients in areas in which louse-borne (epidemic) typhus occurs.

3. Laboratory personnel working with *Rickettsia prowazekii*.

Primary Immunization

Two subcutaneous injections of vaccine 4 or more weeks apart using the dose volume indicated by the manufacturer for adults or for children.

Booster Doses

A single subcutaneous injection of vaccine at intervals of 6 to 12 months for as long as opportunity for exposure exists using the dose volume indicated by the manufacturer for adults or for children. The primary series need never be repeated for booster doses to be effective.

Reactions

Pain and tenderness at the injection site should be expected. A few individuals have reportedly experienced exaggerated local reactions and fever, presumably a manifestation of hypersensitivity.

Contraindications

As is the case for all vaccines propagated in eggs, typhus vaccine should not be administered to anyone who is hypersensitive to eggs.

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YELLOW FEVER VACCINE

INTRODUCTION

At present, cases of yellow fever are reported from only Africa and South America. Two forms of yellow fever – urban and jungle – are distinguishable epidemiologically. Clinically and etiologically, they are identical.

Urban yellow fever is an epidemic viral disease of man transmitted from infected to susceptible persons by a vector, the *Aedes aegypti* mosquito. With the elimination of *A. aegypti,* urban yellow fever has disappeared from previously epidemic foci.

Jungle yellow fever is an enzootic viral disease transmitted among non-human hosts by a variety of mosquito vectors. It is currently observed only in the jungles of South America and Africa, but in the past it extended into parts of Central America as well. Human cases occur by chance. The disease can ostensibly disappear from an area for years and then reappear. Delineation of areas affected depends upon accurate diagnosis and prompt reporting of all cases.

Urban yellow fever can be prevented by eradicating *A. aegypti* mosquitoes. Jungle yellow fever can be prevented in humans only by immunization. Because infection is from a non-human reservoir, prevention of human cases requires vaccination of all persons at risk.

YELLOW FEVER VACCINE

Yellow fever vaccine is a live, attenuated virus preparation made from one of two strains of virus: 17D and Dakar (French neurotropic). The Dakar strain has been associated with a significant (0.5 percent) incidence of meningoencephalitic reactions and is not recommended. The 17D strain has caused no significant complications.

Licensed vaccine available in the United States is prepared from the 17D strain, which is grown in chick embryo inoculated with a fixed passage level seed virus. The vaccine is freeze-dried supernate of centrifuged embryo homogenate.

Vaccine should be stored at the temperature recommended by the manufacturer until it is reconstituted by the addition of sterile physiologic saline. Unused vaccine should be discarded within approximately 1 hour of reconstitution.

VACCINE USAGE

General Recommendations

Age: Persons 6 months of age or older traveling or living in areas where yellow fever infection exists (currently Africa and South America. (See Vaccination for International Travel).

Special risk: Laboratory personnel who might be exposed to virulent yellow fever virus.

Vaccination for International Travel

To be acceptable for purposes of international travel, yellow fever vaccines must be approved by the World Health Organization and administered at a Yellow Fever Vaccination Center listed with WHO. Vaccinees should have an International Certificate of Vaccination filled in, signed, and validated with the stamp of the Center where the vaccination is administered. (Yellow Fever Vaccination Centers in the United States are designated by the Foreign Quarantine Program of the Public Health Service.*)

Vaccination for international travel may be required under circumstances other than those included in these recommendations. A number of countries in Africa and South America require evidence of vaccination from all entering travelers; some may waive the requirements for travelers coming from non-infected areas and staying less than 2 weeks. These requirements may change, so all travelers should seek current information from health departments and travel agencies.

Some countries require an individual, even if only in transit, to have a valid International Certificate of Vaccination if he has been in countries either known or thought to harbor yellow fever virus. This applies particularly to travelers to South and Southeast Asia by way of the Atlantic.

Primary Vaccination

A single subcutaneous injection of 0.5 ml of reconstituted vaccine for both adults and children.

Revaccination

Yellow fever immunity following vaccination with 17D strain virus has been shown to persist for more than 10 years; the International Sanitary Regulations do not require revaccination more frequently than every 10 years.

Reactions

The few reactions to 17D yellow fever vaccine that occur are generally mild. Five to 10 percent of vaccinees have mild headache, myalgia, low-grade fever, or other minor symptoms 5 to 10 days after vaccination. Symptoms cause less than 0.2 percent to curtail regular activities. Only two cases of encephalitis have been reported in the United States, for more than 34 million doses of vaccine distributed.

Because yellow fever vaccine is prepared from chick embryos, it may induce reactions of varying degrees of severity in individuals hypersensitive to eggs. Experience in the Armed Forces suggests that allergy severe enough to preclude vaccination is very uncommon and occurs only in those who are actually unable to eat eggs.

Precautions and Contraindications

Pregnancy: Although specific information is not available concerning adverse effects of yellow fever vaccine on the developing fetus, it is prudent on theoretical grounds to avoid vaccinating pregnant women.

*For a list of such centers, see *Immunization Information for International Travel,* PHS Publication No. 384, available from the Supt. of Documents, U.S. Government Printing Office, Washington, D.C. 20402 at 40 cents.

Altered immune states: Yellow fever vaccine virus infection might be potentiated by severe underlying diseases, such as leukemia, lymphoma, or generalized malignancy, and by lowered resistance, such as from therapy with steroids, alkylating drugs, antimetabolites, or radiation; therefore, vaccination of such patients should be avoided.

Allergy: Documented hypersensitivity to eggs can be contraindication to vaccination. In making the decision to vaccinate despite a history of egg allergy, a physician must weigh three factors: 1) the nature of the history and of the reported hypersensitivity, 2) the relative risk of exposure to yellow fever, and 3), in the case of international travel, the possible inconvenience from disrupted travel plans.

If international quarantine regulations are the only reason to vaccinate a patient hypersensitive to eggs, efforts should first be made to obtain a waiver. A physician's letter which clearly states the contraindication to vaccination has been acceptable to some governments. (Ideally, it should be written under his letterhead and bear the authenicating stamp used by health departments and official immunization centers to validate International Certificates of Vaccination.) Because this is not uniformly true, however, it is prudent for the traveler to obtain specific and authoritative advice from the country or countries he plans to visit. Their embassies or consulates may be contacted. Subsequent waiver of requirements should be documented by appropriate letters.

SIMULTANEOUS ADMINISTRATION OF LIVE VIRUS VACCINES

There are obvious practical advantages to administering two or more live virus vaccines simultaneously. Data from specific investigations are not yet sufficient to develop comprehensive recommendations on simultaneous use, but a summary of current experience, attitudes, and practices provides useful guidance.

It has been generally recommended that live virus vaccines be given at least 1 month apart whenever possible – the rationale for this being that more frequent and severe adverse reactions as well as diminished antibody responses otherwise might result. Field observations indicate, however, that with simultaneous administration of certain live virus vaccines, results of this type have been minimal or absent. (For example, the third dose of trivalent oral poliovirus vaccine, which is recommended during the second year of life, is commonly given at the same time as smallpox vaccination without evident disadvantage.)

If the theoretically desirable 1-month interval is not feasible, as with the threat of concurrent exposures or disruption of immunization programs, the vaccines should preferably be given on the same day – at different sites for parenteral products. An interval of about 2 days to 2 weeks should be avoided because interference between the vaccine viruses is most likely then.

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